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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,681	07/20/2001	Gregory R.D. Evans	UTSC:646US	2530

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,681	EVANS ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-14 and 16-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-14 and 16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 8/11/04 and applicants' arguments and a Declaration filed 5/3/04. Claims 4, 15, 25-46 have been canceled. Claims 1, 2, 5, 6, 11, 12, 14 and 19-24 have been amended. Claims 1-3, 5-14 and 16-24 are pending.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are new grounds of rejection herein that were not necessitated by applicants' amendment and therefore, this action is not final.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It was not executed in accordance with either 37 CFR 1.66 or 1.68. Specifically, Greg Evans signature is not accompanied by a date.

Response to Argument

Acknowledgement is made of applicants' statement that a new oath for Greg Evans is being prepared and will be filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-14 and 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "administration" in claim 6. There is insufficient antecedent basis for this limitation in the claim. **This is a new rejection necessitated by applicants' amendment.**

Claims 7 and 13 are vague and indefinite in that the metes and bounds of "administration is intravenous, intrathecal, intracavitary and by catheter" are unclear. It is unclear if the administration is intended to be by all of the recited means at once or if applicants intended to recite that the means of administration can be accomplished by any one of the recited methods. If it is the later, it would be remedial to recite that the "said administration is selected from the group comprising intravenous, intrathecal, intracavitary and by catheter". **This is a new rejection.**

Claims 1-3, 5-14 and 16-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for regenerating sciatic nerve defects of less than 15 mm in Sprague Dawley rats using PLLA and PLGA conduits, does not reasonably provide enablement for a method for regenerating all nerve tissue using devices comprised of any biodegradable material in which the material comprises genetically transformed cells. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This is a new rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The instant invention is directed towards use of a device in a method for *in vivo* regeneration of nerve tissue. The device is comprised of a biodegradable conduit whose passage is filled with helper cells that are transformed with an expression vector expressing a growth factor. The device is implanted such that each of said openings are adjacent to nerve tissue to stimulate nerve tissue regeneration. The invention utilizes disciplines of molecular biology and clinical technology.

2) **Scope of the invention**. The conduit can be any biodegradable material, the helper cells can be any of a wide variety of genetically transformed cells such as fibroblasts, stem, fat, Schwann, astrocyte, endothelial and ex vivo propagated nerve cells that have been transformed with a variety of stimulatory growth factors such as nerve growth factor or fibroblast growth factor. Furthermore, the invention envisions the incorporation of a "cell kill gene" into the cells such that upon stimulation the cells are killed. The recited use of the conduit is regeneration of

any tissue inclusion of in humans. Hence the scope of the claims is broad as regards types of tissue and defects regenerated and in components capable of use in the defects.

3) **Number of working examples and guidance**. The instant invention is drawn to a biodegradable conduit, which comprises genetically engineered cells expressing neurotrophic growth factors under control of an inducible promoter. Manufacture characteristics and functional assessments of PLLA used in the conduits were analyzed using *in vitro* assays and *in vivo* animal models (page 43-48). For *in vivo* animal models, Sprague Dawley rats with right sciatic nerve defects were implanted with 12 mm PLLA conduits. Functional and histological assessments of the rats were performed at the end of 16 weeks and compared to autogenous nerve isografts. The isografts were said to be "statistically lower" which is presumed to be a description of functional assessments in all cases except in measuring the weight of the gastrocnemius muscle, which was statistically increased in the autogenous isografts. At the end of 8 months, there was said to be no differences between the isograft controls and experimental animals functionally or histologically except the number of axons/mm2, which was lower in the controls (see pages 43-48).

Dermal Fibroblasts (DFBs) were then engineered to release NGF *in vitro* and *in vivo*. The dermal fibroblasts were transfected with a pIND vector comprising NGF under control of the muristerone promoter. The amount of NGF produced following treatment with muristerone A was assessed (page 49-55). NGF release *in vivo* was said to be determined by using implanted collection chambers filled with induced transfected dermal fibroblasts and the amount of NGF in the collected chambers was assessed (figure 8). However, the effects of the conduits coupled with the engineered cells were not determined.

4) **State of Art**. Enormous efforts have been directed toward developing potential therapies for nerve regeneration. Engineering strategies for peripheral nerve repair have focused on the development of guidance channels such as the development of natural or synthetic tubular nerve guidance channels as alternative to autologous nerve grafts. Only a few devices, Type I collagen and SalumeMedical's Nerve Cuff, have been used to correct for defects of several millimeters (see e.g. Schmidt and Leach, page 299, paragraph 1). However, this approach is said to be limited when the lesion is too large or for regenerating spinal cord damage. Therefore, the effectiveness of the conduits has been limited to date to small defects in peripheral nerve.

Alternative materials that have been analyzed for conduit formation include autologous or non-autologous nerve grafts, synthetic and biodegradable polymers such as PLA and PLGA (Hudson et al, page 621, col 1, paragraph 3). However, Hudson teaches that none of the tested materials to date have surpassed the effectiveness of the nerve autograft. Therefore, researchers have moved to contemplation of bioengineering approaches. Bioengineering strategies have included use of exogenous neurotrophic factors or stimulation of endogenous neurotrophic factors. Methods of delivering these factors have included osmotic pumps, silicone reservoirs, microencapsulation with polymers and expression from viral vectors. Other strategies have included cellular therapies such as use of cellular transplants and genetically engineered cell lines into the site of injury (see for Review of these approaches, Schmidt et al, Annual rev Biomed Eng, 2002). The instant invention proposes as a method of treatment use of biodegradable conduits comprising genetically transformed cells expressing neurotrophic factors for the regeneration of nerves.

5) **Unpredictability of the art**. The art of nerve therapy based upon use of genetically engineered cells is a highly unpredictable art for several reasons.

First, to date regeneration has been limited to repair of small defects in peripheral tissue. "The largest limitation of the existing techniques is the current length of the nerve gap that can be reconstructed" (Hudson, page 624, col 2, paragraph 3). Evans et al teach "we have been limited by the length of a nerve conduit that can support axonal proliferation (10-15 mm)" (page 3, paragraph 1). Regeneration of larger defects as well as defects in the central nervous system is highly unpredictable due to the complexity of the nervous systems (see Schmidt, page 297-300).

Second, successful regeneration using conduits has been demonstrated in animal models for which clinical success in humans is unknown. To this end Evans teaches, "Most of the supportive research has been conducted in the rat or mouse model, however, what may occur in the animal model may be completely different in humans" (page 3, paragraph 1). The success of *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment in humans, *in vitro* results have rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. Ginis and Rao describe the obstacles to comparing the effectiveness of cell transplantation using animal models as predicators of success in humans. The se are summarized as the following a) major differences between equivalent stem and progenitor populations exist when human and rodent or primate cells are compared, b) physiological and biological differences in the response of transplanted cells to the host environment, c) response to growth factors are different in each model, d) transplant and surgical differences, e) differences in the immunological response f) allelic variability in humans. These

factors increase the unpredictability of the instant invention (see Ginis and Rao, page 62, col 1, paragraph 2).

Third, despite extensive research to identify conduits that are comprised of alternative materials, the effectiveness of the nerve autograft has not been significantly surpassed (see Hudson and Schmidt as cited above). Applicants recite broadly that the material can be any biodegradable polymer and exemplify specifically use of PLLA and PLGA (claim 3). Analysis of biomaterial for use in nerve grafts has demonstrated that a great number of these biomaterials are limited by the host immune response to them. The implantation of a biomaterial initiates a sequence of events akin to foreign body reaction (Babensee et al, page 114, col 2). This response starts with an acute inflammatory response, leading to a chronic inflammatory response. These response have included a tissue reaction as well as non-specific foreign body reactions comprised of polymorphonuclear leukocytes and foreign body giant cells, cell damage and necrosis (see e.g. page 115, col 1 last paragraph through page 118, paragraph 10 as well as scarring and construction of regenerated tissues (see e.g. page 122, col 2). Finally, the response of surrounding fibrous tissue is to ultimately function as a barrier to nutrient and product diffusion (see e.g. page 115, col 1). Applicants own data has demonstrated that PLGA is insufficient, "Elongation and partial collapse, however, led to a search for a different polymer as an alternative conduit for guided nerve regeneration" (Evans, 1999, [age 1110, col 2, paragraph 3). In this study, PLLA was demonstrated to be sufficiently stronger and stiffer. The instant specification also teaches that PLLA alone is essentially equivalent to isografts in Sprague Dawley rats functionally and histologically.

Fourth, use of the device in humans is hampered by immune responses to the conduit material and the transplanted cells. Specifically, Babensee et al, teach that the combination of host response to the biomaterial and transplanted cells are compounded. "Taken together, the host response to the polymer microcapsules containing live cells may be viewed as an inflammatory response to the biomaterial and an immune response to the transplanted cells (see page 124, col 2, last paragraph).

Fifth, several sources of cells have been analyzed, none have proven adequate. Autologous grafts or autologous cell sources are preferred. However, these procedures require the ability to harvest appropriate cells from the host. Hudson teaches that it is uncertain whether these cells can be easily isolated from the patient (page 623, col 2, paragraph 2). Grafts using primary cell lines was insufficient (Maysinger et al, 1995, page 23, col 1) as expansion of the cells was problematic in fact not all cell types are able to be expanded in culture to significant number for transplantation. While the use of cell lines overcomes some of these issues, uncontrollable proliferation of transplanted cell lines is a safety concern (Maysinger. page 23, col 1). Transplanted cells from cell lines continue to divide leading to tumor formation as well as revert to wild-type state thus ceasing to synthesize the transgene (page 22, col 2).

6) **Summary**. The invention recites a complex series of methods for regeneration of nerve tissue in humans. The method proposes the grafting of biodegradable conduits filled with cells transformed with expression vectors for the expression of growth factors such that tissue growth is stimulated by the growth factors. The unpredictability of using the claimed invention due to the limitations of size and location of defects, the unpredictability of predictive success of the animal models, immunological responses to the biomaterials and cells, and lack of success to

date of alternative polymers as well as controlled use of transplanted cells together represent a highly unpredictable art. In view of predictability of the art to which the invention pertains: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 9-10 of the amendment filed 5/3/04. Applicants argue the following. 1) The examiner has provided an analysis of five different Wands factors and thus the analysis is incomplete. 2) The examiner has questioned whether or not the invention will work without supporting evidence. To this end, applicants have requested either submission of an affidavit under 37 CFR 1.104(d)(2) or that the rejection be withdrawn. 3) Finally applicants have provided a Declaration under 37 CFR 1.132 from Dr. Evans. The Declaration summarizes data from Sprague Dawley rats of use of PLGA and PLLA conduits with 15 mm right sciatic nerve defects and expression of NGF from DFBs also presented in the instant application. Applicants advance the data presented in the instant application by inclusion of date conducted in nude rats that demonstrate *in vivo* expression of NGF from genetically modified DFB cells using a vector expressing NGF under control of the muristerone promoter. Furthermore, applicants have demonstrated *in vitro*

the ability to express NGF under an inducible promoter in HEK-293 cells and PC12 cells to potentially overcome the problems associated with use of DFBs such as scar formation and transient expression.

Applicants' arguments filed 5/3/04 have been fully considered but they are not persuasive. 1) The instant claims have been rejected under 35 USC 112, first paragraph for lack of enablement, which has been based upon a thorough analysis of the Wands factors. Presentation of five categories that are inclusive of all seven Wand's factors, does not in itself make the analysis incomplete. Rather, the analysis has been summarized above with the most salient issues presented. 2) This office action has expanded upon original arguments in the enablement rejection to respond to applicants need for evidence supporting the rejection. The arguments are based upon knowledge in the art and not personal knowledge and therefore a Declaration under 1.104(d)(2) is not necessary. 3) The Declaration under 37 CFR 1.132 filed 5/3/04 is insufficient to overcome the rejection of claims 1-3, 5-14 and 16-24 based upon 35 USC 112, first paragraph as set forth in the last Office action because: it fails to set forth facts that demonstrate the feasibility of using the recited device to regenerate nerve tissue. The enablement rejection has set forth that the model is only predictive of repair of sciatic nerve defects of less than 15 mm in Sprague Dawley rats using PLLA and PLGA. There is no indication that the devices comprised of genetically transformed cells would not scar or be rejected or lead to uncontrolled cell growth even in animal models. Use of nude rats is not a good model as a predictor of this as the immune system is dysfunctional. Given the preponderance of evidence that such devices are subject to immunological responses by the host system and that the use of transplanted cells are unpredictable, neither the Declaration nor the

specification provide adequate evidence that the instant invention would be able to overcome these obstacles. Furthermore, given the relevant art that teaches that the animal models are not predictive, use of the instant invention in humans is highly unpredictable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7 and 16-18 and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hadlock et al (US 2001/0031974 A1; see entire document) in view of Rohrer et al (Cell Transplantation, 1996, pages 57-68; see entire document) or Blesch et al (J Neurosci Res, 2000, Vol 59:402-409; see entire document) as evidenced by Yee et al (US 6,133,027).

This is a new rejection.

The instant claims have been rejected under 112, first paragraph for lack of enablement. The enablement rejection is based upon a method of regenerating all nerve tissue in humans. The following art rejection is based upon peripheral nerve regeneration in non-human subjects i.e. rats.

The invention recites a nerve tissue conduit that is comprised of a biodegradable conduit with helper cells transformed with an expression cassette comprising a promoter active in said cells that directs expression of a growth factor.

Hadlock et al teach a neural regeneration conduit that is porous and can be comprised of PLGA or PLLA (see e.g. paragraph 0005). The conduit is formed by rolling a flat sheet of material such as PLGA into a cylinder (see e.g. abstract and paragraph 0005) and includes a layer of cells such as Schwann cells that can be engineered for the over-expression of neurotropic factors or NGF through recombinant expression (see e.g. 0032). The conduits is implanted into a subject such that it is adjacent to nerve tissues (see e.g. 0039-0040).

Hadlock et al do not teach that expression of NGF is from an inducible promoter.

Blesch et al teach that currently gene therapy is limited by the inability to regulate the expression of the transferred gene over time but that regulatable gene expression is important for a number of reasons; it is a simple system that uses only one protein for inducing and repressing, and the small size of the tet transactivator and the regulatable promoter such that it can be packaged into a single vector (see Blesch et al, bridging paragraph page 402-403). Blesch et al teach that neurite outgrowth can be modulated using a tetracycline –repressible gene therapy vector for expression of NGF. The vector of Blesch et al is based upon pLXSN, which comprises a tetracycline regulatable promoter, polyA sequences and a selectable/ screenable neomycin marker (see e.g. figure 1 and page 403, col 2, paragraph 2-3). Rat fibroblast cells were transfected with the vector encoding NGF and expression was induced for up to 72 hours (see e.g. page 404, col 1, paragraph 3). Blesch et al teach administration of the tet-regulated system in cell culture. Yee et al teach that for *in vivo* administration, tetracycline is administered by among other means intravenous (see e.g. col 17, line 26-36).

Rohrer et al teach methods of neural transplantation of genetically modified cells to reverse neurodegenerative disorders (see e.g. abstract). The genetically modified cells are PC12

nerve cells transfected with pNGF-MEP 4 (see e.g. page 58, col 2, paragraph 1). PNGF-MEP 4 comprises the NGF coding sequence inserted into pMEP4, which is a zinc-inducible human metallothionein promoter, and an SV40 polyadenylation sequence and the hygromycin selectable/ screenable marker (see e.g. page 58, col 1, paragraph 3). The cells were implanted into rats and the rats were fed zinc for 5 weeks.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express NGF in nerve conduits as taught by Hadlock et al using the inducible promoters taught by Blesch et al and Rohrer et al because Hadlock et al teach that it is within the ordinary skill of the art to recombinantly express NGF ex vivo transformed cells in nerve conduits but do not expressly indicate the type of promoter to use and because Blesch et al and Rohrer et al teach that it is within the ordinary skill in the art to express NGF therapeutically using inducible promoters. One would have been motivated to do so in order to receive the expected benefit of regulated expression of desired genes that is inherent in inducible promoter use as well the tetracycline repressible vector system is a simple system that uses only one protein for inducing and repressing and because packaging of the tet-transactivator and the regulatable promoter into the single vector is possible (see Blesch et al, bridging paragraph page 402-403) while the zinc inducible promoter has minimal leakiness and high inducibility (see Rohrer et al, page 61, col 2, last paragraph). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hadlock et al (US 2001/0031974 A1; see entire document) in view of Blesch et al (J Neurosci Res, 2000, Vol 59:402-409; see entire document) or Rohrer et al (Cell Transplantation, 1996, pages 57-68; see entire document) further in view of Pochon et la (Human Gene Therapy, 1996, vol 7, pages 851-860) or Wolfe et al (US 2003/015071; see entire document). **This is a new rejection.**

The instant claims have been rejected under 112, first paragraph for lack of enablement. The enablement rejection is based upon a method of regenerating all nerve tissue in humans. The following art rejection is based upon peripheral nerve regeneration in non-human subjects i.e. rats.

The invention recites a nerve tissue conduit that is comprised of a biodegradable conduit with helper cells transformed with an expression cassette comprising a cell kill gene.

The teachings of Hadlock, Blesch and Rohrer et al are as above except none of the references teach the inclusion of cell kill genes.

Pochon et al teach intrathecal delivery of genetically modified BHK cells into rats and sheep (see e.g. abstract). The cells were transformed with an expression vector, pNUT, comprising CNTF under control of the methallothionein promoter. The vector furthermore comprised a thymdine kinase gene, which comprises the hsv tk promoter by definition, for destroying the transplanted cells in the event of device breakage leading to tumor formation (see e.g. page 855, col 2, paragraph 6). In the presence of tk, the cells are sensitive to nucleoside analogues such as ganciclovir. The effect of ganciclovir was assessed in culture. However, it is presumed that *in vivo* delivery would have occurred intrathecally given the establishment of this protocol for delivery of the cells.

Wolfe et al teach use of a killer gene under control of an inducible promoter such that induction of its expression results in cell death (see e.g. paragraph 2). Cells that differentiate into undesired cells are killed by induction of the promoter (see e.g. paragraph 59).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include cell kill genes in *ex vivo* engineered cells as taught by Pochon et al and Wolfe et al for placement in nerve conduits as taught by Hadlock et al because Wolfe et al and Pochon et al teach that it is within the ordinary skill of the art to incorporate cell kill gene sequence into vectors for transformation into cells to be transplanted and because Hadlock et al teach that it is within the ordinary skill in the art to incorporate genetically engineered cells in nerve conduits for implantation. One would have been motivated to do so in order to receive the expected benefit of the ability to deleted transformed cells from the subject if the cells escape their environment and become tumors or differentiate into undesired cell types. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 102 and 103 on pages 11-13 of the amendment filed 5/23/04. Applicants argue that Hadlock fails to disclose use of a recombinant vector for generation of cells to express a growth factor. Secondly, applicants argue that there is insufficient motivation in Hadlock to select inducible promoters.

Applicants' arguments filed 8/11/04 have been fully considered but they are not persuasive. In fact Hadlock does consider using a recombinant vector in the cells as described in paragraph 0032. Use of inducible promoters is well established in recombinant vectors for controlled expression of transgenes as described by Blesch et al and Rohrer et al. The motivation to combine Hadlock et al with Blesch et al and Rohrer et al is found in the secondary references as detailed above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1636

November 21, 2003

GERRY LEFFERS
PRIMARY EXAMINER